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CENTER FOR BIOLOGICS EVALUATION AND RESEARCH
Biostatistics Branch (HFM-215)

Biostatistical Review Memorandum

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FROM: *Jawahar Tiwari, Ph.D.*

THROUGH: *Peter A. Lachenbruch, Ph.D., Chief*

SUBJECT: *Filgrastim for the reduction in the duration of neutropenia in the treatment of acute myeloid leukemia.*
Submission dated September 27, 1996

TO: *Henry Chang, M.D.*
Division of Clinical Trial Design and Analysis (HFM-570)

CC: HFM-99/Document Control Center: PLA 96-1136
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BACKGROUND

The study supporting this indication was designed as a randomized, double-blind, placebo-controlled, multicenter (Europe and Australia) Phase 3 trial enrolling a total of 521 patients (262 in placebo and 259 in Filgrastim). The randomization was stratified by center and age <50 years and ≥ 50 years). Patients were to received 1 or 2 courses of induction chemotherapy and then, if in remission (≤ 5% myeloplasts in the bone marrow), 1 or 2 courses of consolidation chemotherapy. Patients were randomized to receive Filgrastim or placebo between days 6 and 8 of induction chemotherapy.

The primary efficacy endpoint was defined as the duration of neutropenia. The protocol also specified "the remission rate" as the primary safety endpoint. The time to disease progression, survival time, incidence and duration of fever (oral temperature $\geq 38^0$ C), intravenous(IV) antibiotic use, the incidence of documented infection, and the duration of hospitalization were specified as important secondary endpoints.

The protocol called for interim analyses (using double triangular plan) of the primary safety endpoint (complete remission rate) after accrual of 60 patients in each arm.

The maximum sample size of 554 patients was estimated to provide at least a 90% probability of detecting a 15% absolute difference in the remission rate between the two arms at a significance level of 0.05. The placebo remission rate was assumed to be 65%.

Interim Safety Analyses

> "An interim safety report was prepared after the results of remission induction in each group consecutively randomized patients became known. Each report was based on summary data submitted to Amgen Ltd on an ongoing basis relating to registration, randomization and remission status. The data presented in the report was blinded. However, A/B unblinded information was available for review by an independent Data Monitoring Committee. Data on disease progression and survival were collected at 6 monthly intervals from randomization of each patient and Kaplan-Meier survival curves were prepared."

Data Monitoring Committee

> "An independent Data Monitoring Committee (DMC) was constituted to review the data presented in each interim safety report as assess whether there was any safety concern or overwhelming evidence of a treatment effect which would have necessitated that the trial be discontinued or amended. The Committee comprised the following:
>
> Prof David Linch, Professor of Hematology (Chairman), University College, London, UK
> Dr David Machin, Senior Statistician, MRC Clinical Trials Unit, Cambridge, UK
> Dr Peter Taylor, Consultant Hematologist, Rotherham District Hospital, UK
> Dr Nydia Testa, Experimental Hematologist, Christie Hospital, Manchester, UK"

DMC Decisions

"The decisions of the DMC from Interim analysis 1 to 4 were that the study should continue. Following presentation of the results of the fifth interim analysis, the DMC noted that it was possible that there was no difference in the complete remission rate of the two arms and that this was an important negative result which implied that there was no immediate safety concern of using Filgrastim in AML. However, the DMC recommended that the trial continue since it was possible that if study was stopped at this stage, that when the results of the further 94 patients already in induction were added, this could lead to an inconclusive result of the study."

"Following Interim Analysis 7 the Committee stated that there were no safety reasons to stop the trial and there were enough patients to provide a conclusive answer about the primary safety endpoint. After communicating the decision of the DMC to the investigators and allowing patients that had already given consent to be randomized, the trial, the trial was closed to patient randomization on 7 October 1994. All patients were followed until completion of protocol."

COMMENTS

1. Remission Rate (the primary safety endpoint)

The observed remission rates in Filgrastim and placebo groups are given in Table 1. There is no significant difference between the two arms.

Table 1. The primary safety endpoint: Remission rate.

Safety Variable	Filgrastim	Placebo	Treatment Difference (95% CI)	P-value*
Remission Rate	178/259 (68.7%)	177/262 (67.6%)	1.2% (-6.8%, 9.2%)	0.77

* Fisher's Exact test

2. Time to Disease Progression

The median time to disease progression was compared in all patients and also in subsets defined by patients ≤ 55 years and patients between 56 and 70 years of age. The estimates of median, associated 95%CI and log-rank P-values are given in Table 2. There was no significant difference between Filgrastim and placebo in any comparison. However, the median time to disease progression was higher in placebo groups for all age categories.

Table 2. Time to disease progression (days).

Age Group	Filgrastim		Placebo		DIFFERENCE	P**
	N	Median# (95% CI)	N	Median# (95% CI)	Median (95% CI*)	
ALL	259	165 (133, 237)	262	186 (154, 233)	-21 (- 71, 47)	0.87
$\leq$ 55	139	203 (139, 297)	137	253 (180, 321)	-50 (-149, 61)	0.89
56 - 70	95	153 (68, 252)	110	169 (124, 212)	-16 (- 74, 41)	0.85

\# Kaplan-Meir estimate
* bootstrap estimate
** log-rank test

3. Patient Survival

The patient survival was compared in all patients and also in subsets defined by patients ≤ 55 years and patients between 56 and 70 years of age. The estimates of median, associated 95%CI and log-rank P-values are given in Table 3. There was no significant difference between Filgrastim and placebo with for any comparison. As in the case of time to disease progression, the median survival time was higher in placebo groups for all patients and patient ≤ 55 years of age.

Table 3. Patient survival (days).

Age Group	Filgrastim		Placebo		DIFFERENCE	P**
	N	Median (95% CI)	N	Median (95% CI)	Median (95% CI*)	
ALL	259	380 (331, 438)	262	425 (372, 475)	-45 (-107, 27)	0.83
≤ 55	139	409 (368, 598)	137	491 (426, 646)	-82 (-202, 126)	0.78
56 - 70	95	350 (192, 438)	110	349 (233, 430)	1 (-170, 136)	0.92

\# Kaplan-Meir estimate
* bootstrap estimate
** log-rank test

4. The Duration of Neutropenia

The duration of neutropenia, the primary efficacy endpoint, was significantly reduced in the Filgrastim arm (median: 14 days in Filgrastim vs 19 days in placebo, Table 4).

Table 4. The primary efficacy endpoint: Duration of neutropenia.

Efficacy Variable	Filgrastim	Placebo	Treatment Difference* (95% CI)	P-value**
Median duration of neutropenia (days)	14.0	19.0	-5.0 (-6.0, -4.0)	0.0001

* Hodges-Lehmann estimate
** Wilcoxon Rank Sum test

5. The Incidence and the Duration of Fever

The results on the incidence and the duration of fever in the Filgrastim and placebo groups are given in Table 5. The incidence of fever did not show a significant difference between the two groups. However, the median duration of fever was 2 days shorter in the Filgrastim arm (P=0.009).

Table 5. The secondary efficacy variable: The incidence and the duration of fever.

Efficacy Variable	Filgrastim	Placebo	Treatment Difference* (95% CI)	P-value
Incidence of fever	235/259 (90.7%)	242/262 (92.4%)	-1.6% (-6.4%, 3.1%)	0.532*
Median duration of fever (days)	7.0	9.0	-2.0** (-3.0, 0.0)	0.009#

* Fisher's Exact test
** Hodges-Lehmann estimate
\# Wilcoxon Rank Sum test

6. The Incidence and the Duration of non-prophylactic IV antibiotic usage

The results on the incidence and the duration of non-prophylactic IV antibiotic usage are given in Table 6. The median duration of the non-prophylactic IV antibiotic usage was reduced by 4 days in the Filgrastim group (P=0.0001). The incidence of the non-prophylactic IV antibiotic usage was almost identical in both treatment arms, however Table 6).

Table 6. The secondary efficacy variable: The incidence and the duration of non-prophylactic IV antibiotic usage.

Efficacy Variable	Filgrastim	Placebo	Treatment Difference (95% CI)	P-value
Incidence of non-prophylactic IV antibiotics	247/259 (95.3%)	251/262 (95.8%)	-0.5% (-4.0%, 3.1%)	0.834*
Median duration of non-prophylactic IV antibiotics (days)	15.0	19.0	-4.0** (-5.0, -2.0)	0.0001#

* Fisher's Exact test
** Hodges-Lehmann estimate
\# Wilcoxon Rank Sum test

7. The Incidence of documented (microbiologically defined) infections

The observed incidence of documented infection in the Filgrastim group was 37.1% as compared with 36.3% in the placebo group (P=0.856, Table 7).

Table 7. The secondary efficacy variable: The incidence of documented (microbiologically defined) infections.

Efficacy Variable	Filgrastim	Placebo	Treatment Difference (95% CI)	P-value*
Incidence of documented infections	96/259 (37.1%)	95/262 (36.3%)	0.8% (-7.5%, 9.1%)	0.856

* Fisher's Exact test

8. The duration of hospitalization

The observed median duration of hospitalization in the Filgrastim group was 20 days as compared with 25 days in the placebo group. The difference between the two arms was statistically significant (P= 0.0001, Table 8).

Table 8. The secondary efficacy variable: The duration of hospitalization.

Efficacy Variable	Filgrastim	Placebo	Treatment Difference* (95% CI)	P-value**
Median duration of hospitalization (days)	20.0	25.0	-4.0 (-6.0, -3.0)	0.0001

* Hodges-Lehmann estimate
** Wilcoxon Rank Sum test

CONCLUSION

1. The duration of neutropenia, the primary endpoint of the study, was significantly decreased in the patients treated with Filgrastim (median 14 vs 19 days, P=0.0001).

2. This study also showed significant effect of Filgrastim on duration of fever, duration of non-prophylactic IV antibiotic usage, duration of hospitalizations (all secondary endpoints).

3. The remission rate, the primary safety endpoint, did not show significant difference between the placebo and Filgrastim arms. This safety endpoint was monitored by the independent Data Monitoring Committee.

4. The two other very important clinical endpoints - time to disease progression and patient survival - did not show statistically significant difference between the two arms.

However, it is of some concern that the observed median survival was lower (45 days) in the Filgrastim-treated patients. A similar negative trend was observed with respect to "time to disease progression"; here the median time to progression was lower (by 21 days) in Filgrastim patients